Respiratory Medicine (2007) **101**, 850–853

ELSEVIER

respiratoryMEDICINE

SHORT COMMUNICATION

Does beta-blocker treatment influence central sleep apnoea?

Thomas Köhnlein*, **Tobias Welte**

Department of Respiratory Medicine, Medizinische Hochschule Hannover (Hannover Medical School), Carl-Neuberg-Strasse 1, D-30625 Hannover, Germany

Received 29 September 2006; accepted 27 November 2006

KEYWORDS
Beta-blocker;
Central sleep apnoea;
Cheyne–Stokes respiration;
Heart failure

Summary
Chronic severe heart failure is frequently associated with disturbances in the central control of breathing. During wakefulness, central breathing disorders could be ameliorated with beta-blocker treatment, but nothing is known about the effects of beta-blockers on the control of breathing during sleep. This study intends to determinate the prevalence and severity of nocturnal apnoeas and hypopnoeas in heart failure patients treated with or without metoprolol or carvedilol.
Fifty consecutive patients with dilated cardiomyopathy in NYHA class II–IV with a left ventricular ejection fraction (LVEF) of 35% or below were studied with full polysomnography over one night.
The mean Apnoea–Hypopnoea Index of beta-blocker free patients was 19.8 ± 14.2 versus 7.4 ± 8.5 ($p < 0.05$) and 8.7 ± 8.1 ($p < 0.05$) in patients treated with metoprolol or carvedilol, respectively. The arousal index, sleep quality, and daytime sleepiness were improved in similar magnitude.
Conclusion: Long-term treatment of patients with advanced chronic heart failure with sufficient doses of metoprolol or carvedilol is associated with a lower prevalence and severity of central sleep apnoea (CSA).

Introduction

About 20–40% of patients with advanced chronic heart failure suffer from central breathing disorders.[1] It had been suggested that heart failure might be causally related with alterations in the central control of breathing, resulting in

*Corresponding author. Tel.: +49 511 532 3533; fax: +49 511 532 8532.
E-mail address: thomas.koehnlein@web.de (T. Köhnlein).

0954-6111/$ - see front matter © 2006 Published by Elsevier Ltd.
doi:10.1016/j.rmed.2006.11.023

periodic breathing during the day and/or Cheyne–Stokes respiration during sleep.[2] Disorders in the central control of breathing may be a powerful, independent predictor for premature dying.[3,4]

During wakefulness, periodic breathing may appear spontaneously, or might be provoked by exercise.[5] During sleep, the typical pattern of Cheyne–Stokes respiration can be detected during light sleep stages, and is referred to as central sleep apnoea (CSA).[6]

Long-term treatment with beta receptor blocking substances (beta-blockers) reduces the inappropriate increase of ventilation during exercise and alleviates the central breathing disorders during wakefulness.[7,8] This resulted in improved exercise capacity and slower progression of the underlying heart disease.[9] Until today nothing is known about the effects of beta-blocker treatment on sleep-related central breathing disorders.

We hypothesized that long-term application of beta-blockers in patients with advanced dilated cardiomyopathy influences nocturnal central breathing disorders, thereby improving CSA.

Patients and methods

Stable chronic heart failure patients with dilated cardiomyopathy in NYHA class II–IV with a left ventricular ejection fraction (LVEF) of 35% or below, were studied. 'Stable' was defined as no requirement for changes in the cardiac medication, including diuretics, within a 6 months period prior to polysomnography. Patients with or without beta-blocker treatment were considered. The remaining medication had to be in accordance with the Guidelines of the European Society of Cardiology.[10]

Patients with uncertain compliance, obstructive sleep apnoea (more than 5 obstructive apnoeas per hour of sleep), restless legs syndrome or periodic limb movement syndrome, insomnia, co-medication with sedative effects, implanted cardiac pacemaker, previous stroke, cardiac valvular defects, uncontrolled diabetes, or other concomitant disease with possible influence on the control of breathing were not included. Patients with contraindications for beta-blockers (chronic obstructive pulmonary disease, moderate or severe peripheral arterial insufficiency in Fontaine Stage II–IV) were excluded to prevent an overrepresentation of these patients in the control group.

The patients' medical regimen in the previous 6 months was taken from the complete clinical notes. The compliance to the medical treatment had to be confirmed by each patient. At study entry, daytime sleepiness was assessed with the Epworth sleepiness scale,[11] and polysomnography was performed over one night.

LVEF was determined by ventriculography during cardiac catheterization and was recently confirmed by echocardiography.

Full polysomnography was performed and scored in accordance with international standards [12–14] by the same person who was blinded for the medication of the patients. The diagnosis CSA was established when at least 90% of all detected respiratory events were of central origin.

The criterion for the diagnosis and the severity of the sleep apnoea was the apnoea hypopnoea index (AHI), which was a continuous variable and the primary outcome parameter. The statistical analysis was performed with ANOVA and the Kruskal–Wallis Test, if appropriate. Post hoc analysis applied the Dunnett-*t*-test (SPSS-software Version 13.0, SPSS Inc., Chicago, IL, USA). A $p<0.05$ was considered significant.

This study was approved by the local ethics committee. Patients gave their written informed consent prior to inclusion into the study.

Results

Within a period of 14 months, 185 consecutive cases were screened. Fifty patients fulfilled all in- and exclusion criteria and agreed to participate in this study. In 5 patients, previously undetected obstructive sleep apnoea was found,

Table 1 Anthropometric, functional and polysomnographic data from 45 patients with advanced dilated cardiomyopathy without (reference group) or with long-term beta-blocker treatment (metoprolol or carvedilol).

	Reference group ($n=16$)	All patients on long-term beta-blocker treatment ($n=29$)
Age (years)	58.1±10.2	53.8±10.5
Aetiology of dilated cardiomyopathy ischaemic/idiopathic/unknown, *n*	12/4/0	18/9/2
NYHA functional class II/III/IV, *n*	7/7/2	13/13/3
Left ventricular ejection fraction (%)	25.9±8.1	26.1±7.9
Epworth sleepiness score	11±4	7±4
Apnoea–hypopnoea index	19.8±14.2	8.0±8.2*
Arousal index	22.4±13.8	9.5±7.5**
Sleep period time (SPT) (min)	328.4±46.1	332.7±53.7
Total sleep time (TST) (min)	236.3±61.5	283.0±68.5
Wake (% SPT)	28.8±12.0	15.9±11.6**
Sleep stage 1 (% SPT)	18.3±9.5	15.2±10.6
Sleep stage 2 (% SPT)	32.1±15.0	33.0±9.6
Sleep stage 3 (% SPT)	6.6±4.6	10.6±6.3
Sleep stage 4 (% SPT)	9.0±6.3	12.4±8.6
Rapid eye movement (REM) (% SPT)	5.3±4.2	13.0±6.2**
Mean SaO_2 during TST (%)	93.8±2.2	95.0±1.6
$SaO_2<90\%$ (% SPT)	10.6±17.6	2.2±5.2*
Periodic limb movement index	1.8±1.2	2.0±0.9

Data represent mean±standard deviation (SD). Beta-blocker treatment is associated with a significantly reduced frequency of apnoeas and hypopnoeas during sleep, improved sleep time, improved sleep quality, and better oxygenation. Statistical significant differences between the treatment groups and the reference group are indicated with asterisks (* $p<0.05$; ** $p<0.01$). NYHA = New York Heart Association.

and these subjects were excluded from further analysis. The remaining 45 patients (38 male, 7 female) suffered from ischaemic, idiopathic, or undetermined dilated cardiomyopathy ($n = 30$, 13, and 2 patients, respectively). Anthropometric data and further details are shown in Table 1 and in the Online supplement.

Sixteen patients were without beta-blocker treatment since more than 6 months (reference group). Previous beta-blocker treatment was terminated due to symptomatic bradycardia, fatigue or impotence in 14 patients. In two cases the reasons were unclear. The remaining 29 patients were on regular and sufficient doses of metoprolol ($n = 16$), or carvedilol ($n = 13$). Eighteen out of 45 patients (40%) had CSA with an AHI $\geqslant$ 15.

In the reference group, CSA was found in 11 patients (69%). In this group, the mean AHI was 19.8 ± 14.2, the mean arousal-index was 22.4 ± 13.8, and the mean Epworth sleepiness score was 11 ± 4.

In patients with beta-blocker treatment, CSA was established in 7 out of 29 patients (24.1%; $p < 0.05$). The overall AHI was 8.0 ± 8.2 ($p < 0.05$), the arousal-index was 9.5 ± 7.5 ($p < 0.01$), and the mean Epworth sleepiness score was 7 ± 4 ($p < 0.05$).

Subgroup analyses revealed no significant differences between patients treated with metoprolol or carvedilol (Online supplement).

Discussion

Our data show that patients with moderate to severe dilated cardiomyopathy have a high prevalence of CSA. Sub-dividing of the patients into those with or without continuous beta-blocker treatment revealed that the prevalence and severity of CSA was significantly lower in patients with long-term treatment with carvedilol or metoprolol.

This is the first study investigating the relation between beta-blocker treatment and the prevalence of CSA in chronic heart failure patients. Our patients represent a homogeneous group with nearly pure CSA. The overall prevalence of 40% CSA is in accordance with previously published data.[1]

The differences in the severity of CSA between beta-blocker treated and non-treated patients was of similar magnitude like the improvements with high dose application of oxygen [15] or continuous positive airway pressure (CPAP),[16] the most widespread therapy in CSA. Limited data is available for the effects of assisted pressure controlled ventilation,[17] acetazolamide,[18] and cardiac resynchronization therapy.[19]

The lower Epworth sleepiness scores in patients with long-term beta-blocker treatment are clinically important. They might be explained by improvements in the frequency of arousals and the percentage and duration of uninterrupted periods of the refreshing sleep stages (Table 1).

The physiologic effects of beta-blocker treatment and the influence on the prognosis of chronic heart failure patients need to be assessed in further clinical trials. Our data justify a prospective, controlled, double blind study without the limitations of a retrospective design. Due to the complete absence of historical data, the current authors failed to obtain Ethical approval for a prospective study, which needs to allocate chronic heart failure patients into a beta-blocker-free control group.

In conclusion, this epidemiologic study demonstrates that patients with moderate to severe dilated cardiomyopathy, treated with sufficient doses of the beta-blockers metoprolol or carvedilol, had significantly lower prevalence and severity of CSA. This was associated with better sleep quality and reduced daytime sleepiness.

Acknowledgement

The authors thank Dr. Diane Wieczorek for performing polysomnographies and Dr. Ludwig Hoy for the statistical analysis.

Appendix A. Supplementary materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.rmed.2006.11.023.

References

1. Javaheri S. Sleep disorders in systolic heart failure: a prospective study of 100 male patients. The final report. *Int J Cardiol* 2006;**106**:21–8.
2. Corra U, Pistono M, Mezzani A, et al. Sleep and exertional periodic breathing in chronic heart failure: prognostic importance and interdependence. *Circulation* 2006;**113**:44–50.
3. Leite JJ, Mansur AJ, de Freitas HF, et al. Periodic breathing during incremental exercise predicts mortality in patients with chronic heart failure evaluated for cardiac transplantation. *J Am Coll Cardiol* 2003;**41**:2175–81.
4. Hanly PJ, Zuberi-Khokhar NS. Increased mortality associated with Cheyne–Stokes respiration in patients with congestive heart failure. *Am J Respir Crit Care Med* 1996;**153**:272–6.
5. Piepoli MF, Ponikowski PP, Volterrani M, Francis D, Coats AJ. Aetiology and pathophysiological implications of oscillatory ventilation at rest and during exercise in chronic heart failure. Do Cheyne and Stokes have an important message for modern-day patients with heart failure? *Eur Heart J* 1999;**20**:946–53.
6. Douglas NJ. Control of ventilation during sleep. In: Kryger MH, Roth T, Dement WC, editors. *Principles and practice of sleep medicine*. Philadelphia: Saunders; 1994. p. 201–11.
7. Agostoni P, Guazzi M, Bussotti M, De Vita S, Palermo P. Carvedilol reduces the inappropriate increase of ventilation during exercise in heart failure patients. *Chest* 2002;**122**:2062–7.
8. Malfatto G, Facchini M, Branzi G, Riva B, Sala L, Perego GB. Long-term treatment with the beta-blocker carvedilol restores autonomic tone and responsiveness in patients with moderate heart failure. *J Cardiovasc Pharmacol* 2003;**42**:125–31.
9. Metra M, Nodari S, Parrinello G, Giubbini R, Manca C, Dei Cas L. Marked improvement in left ventricular ejection fraction during long-term beta-blockade in patients with chronic heart failure: clinical correlates and prognostic significance. *Am Heart J* 2003;**145**:200–2.
10. Remme WJ, Swedberg K. Task force for the diagnosis and treatment of chronic heart failure, European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure. *Eur Heart J* 2001;**22**:1527–60.
11. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;**14**:540–5.

12. American Thoracic Society. Indications and standards for cardiopulmonary sleep studies. *Am Rev Respir Dis* 1989;**139**: 559–68.
13. Penzel T, Hajak G, Hoffmann RM, et al. Empfehlungen zur Durchführung und Auswertung polygraphischer Ableitungen im diagnostischen Schlaflabor. *Z Elektroenzephalogr Elektromyogr Verw Geb* 1993;**2**:65–70.
14. Rechtschaffen A, Kales A. *A manual of standardised terminology, techniques and scoring system for sleep stages of human subjects*. Washington DC: US Government Printing Office; 1968 (NIH publication No. 204).
15. Andreas S, Clemens C, Sandholzer H, Figulla HR, Kreuzer H. Improvement of exercise capacity with treatment of Cheyne–Stokes respiration in patients with congestive heart failure. *J Am Coll Cardiol* 1996;**27**:1486–90.
16. Sin DD, Logan AG, Fitzgerald FS, Liu PP, Bradley TD. Effects of continuous positive airway pressure on cardiovascular outcomes in heart failure patients with and without Cheyne–Stokes respiration. *Circulation* 2000;**102**:61–6.
17. Köhnlein T, Welte T, Tan LB, Elliott MW. Assisted ventilation for heart failure patients with Cheyne–Stokes respiration. *Eur Respir J* 2002;**20**:934–41.
18. Javaheri S. Acetazolamide improves central sleep apnoea in heart failure: a double-blind, prospective study. *Am J Respir Crit Care Med* 2006;**173**:234–7.
19. Gabor JY, Newman DA, Barnard-Roberts V, et al. Improvement of Cheyne–Stokes respiration following cardiac resynchronisation therapy. *Eur Respir J* 2005;**26**:95–100.